09856289.032003

OIPE #4
MAR 2 0 2003
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JC194

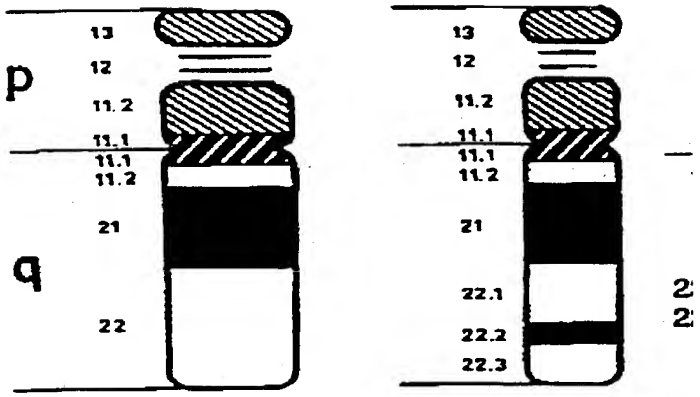

Figure 1

OIPE
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09858289 .032003

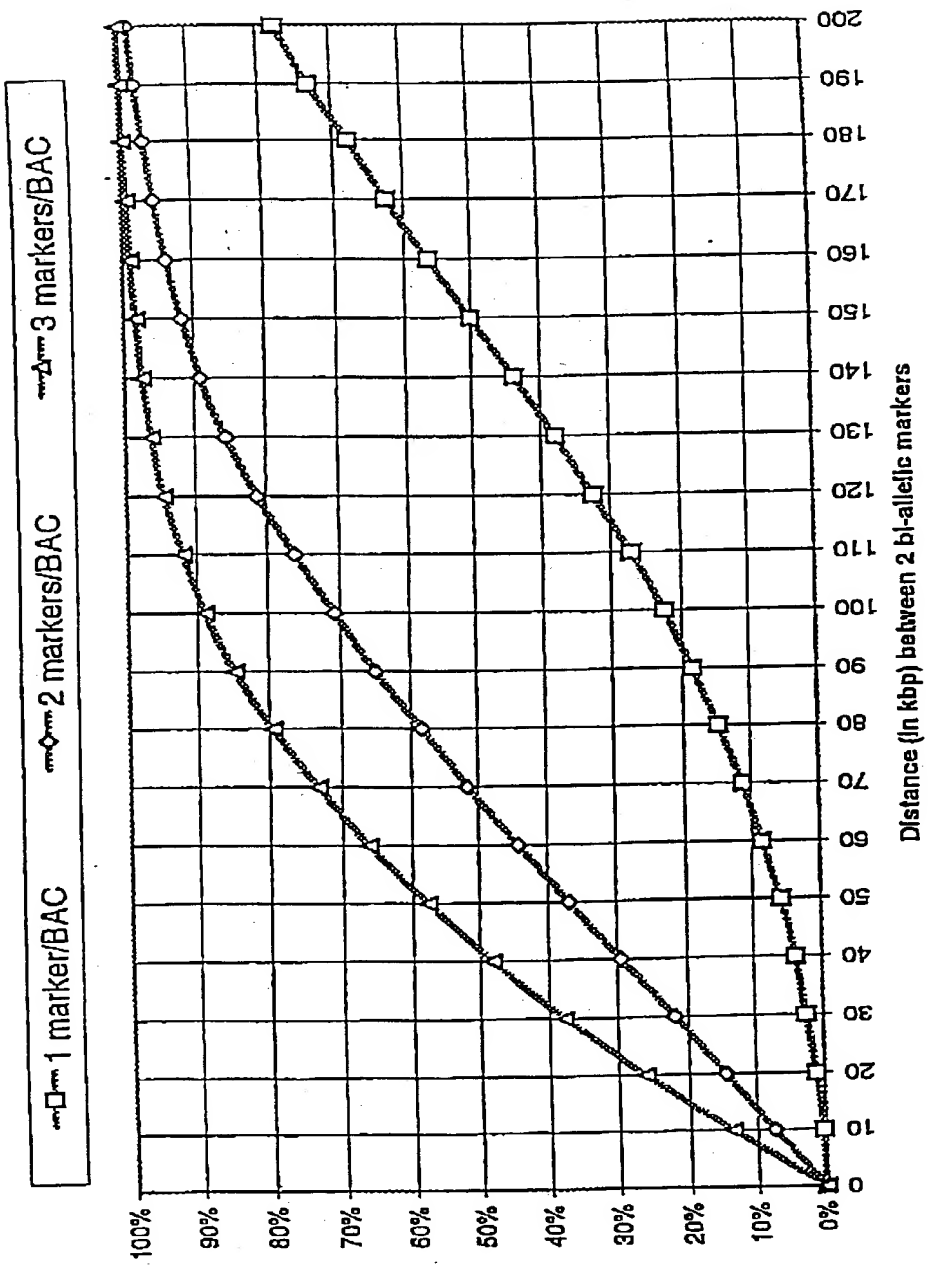

Figure 2A

OIPE
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JC184

09858239.032003

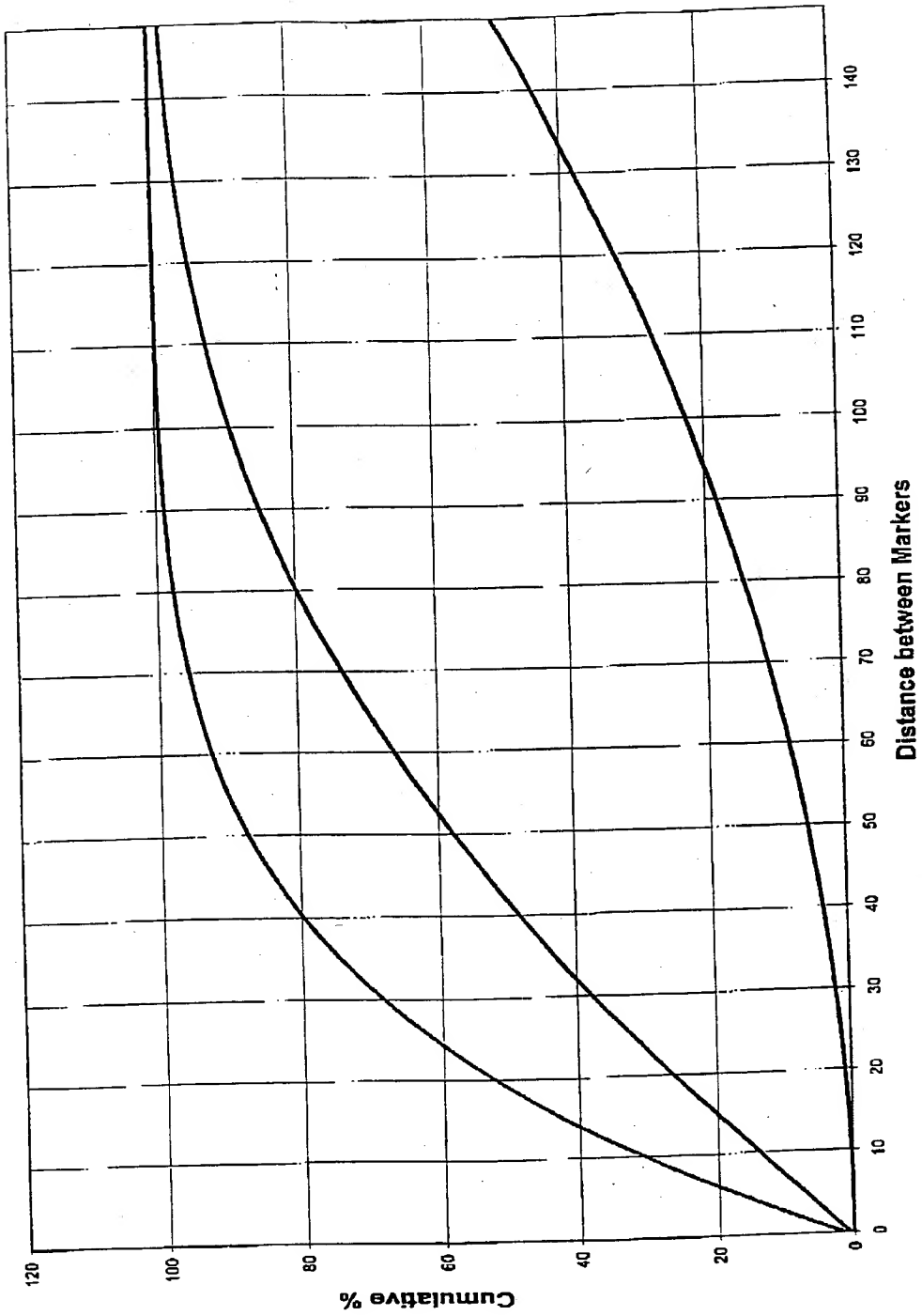
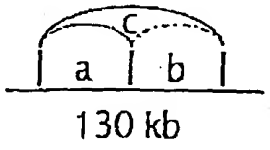


Figure 2B

OIPE JC194 MAR 2 0 2003 PATENT & TRADEMARK OFFICE

LD in a random French caucasian population

- 54 sized « random » BACs covering 8100 kb
- 213 SNP ; 2 to 6 / BAC, mean allele frequency = 0.3
- Order and distance unknown
- For 1 BAC :



  * $\overline{m}$ intermarker distance : 130/3 = 43 kb
  * $\overline{m}$ LD strength estimate : m (a,b,c) = 0.51

- For 54 BACs :
  * $\overline{m}$ intermarker distance = 38 kb
  * $\overline{m}$ LD strength estimate = 0.63 ± 0.05 (324 pairs)
- For 19 unlinked SNPs : m LD strength estimate = 0.12 ± 0.007 (171 pairs)

Figure 2c

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OIPE
JC194

p-VALUE DISTRIBUTION

# aff	150						
# non aff	150						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	8,77E-05	0,06407752	0,14252002	0,19106311	0,21543442	0,22009395
Δ pAi	0,1	1,91E-08	0,00060364	0,00467774	0,01023571	0,01382303	0,01382303
Δ pAi	0,15	3,06E-12	1,3319E-06	3,8827E-05	0,0001478	0,0002343	0,00020218
Δ pAi	0,2	3,22E-16	9,1413E-10	9,0305E-08	5,733E-07	9,6336E-07	5,733E-07
Δ pAi	0,25	2,08E-20	2,2614E-13	6,2679E-11	5,873E-10	8,7113E-10	2,5396E-10
Δ pAi	0,3	7,82E-25	2,152E-17	1,3261E-14	1,5189E-13	1,5189E-13	1,3261E-14
Δ pAi	0,35	1,62E-29	7,9823E-22	8,4152E-19	9,1669E-18	4,2713E-18	5,5844E-20
Δ pAi	0,4	1,73E-34	1,1282E-26	1,524E-23	1,1488E-22	1,524E-23	1,1282E-26

# aff	200						
# non aff	200						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	5,92E-06	0,03250945	0,09039173	0,13111935	0,15260313	0,15678006
Δ pAi	0,1	8,65E-11	7,4765E-05	0,00109084	0,00302686	0,00447365	0,00447365
Δ pAi	0,15	8,02E-16	2,3653E-08	2,0257E-06	1,1771E-05	2,1573E-05	1,7772E-05
Δ pAi	0,2	4,18E-21	1,5375E-12	6,7374E-10	7,764E-09	1,5417E-08	7,764E-09
Δ pAi	0,25	1,13E-26	2,525E-17	4,4025E-14	8,5532E-13	1,4423E-12	2,8149E-13
Δ pAi	0,3	1,47E-32	1,1488E-22	5,8424E-19	1,4886E-17	1,4886E-17	5,8424E-19
Δ pAi	0,35	8,62E-39	1,4784E-28	1,5457E-24	3,6958E-23	1,3394E-23	4,197E-26
Δ pAi	0,4	2,09E-45	5,2308E-35	7,6438E-31	1,1224E-29	7,6438E-31	5,2308E-35

# aff	affected individuals
# non aff	non affected Individuals
pAi non aff	allele frequency in non affected individuals
Δ pAi	% Difference in allele frequency between affected and non-affected individuals

Figure 3 (I)

09550203 - 032003

OIPE
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JC13

p-VALUE DISTRIBUTION

# aff	500						
# non aff	500						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	8E-13	0,00072323	0,00741865	0,0169842	0,02371865	0,02516449
Δ pAi	0,1	1,07E-24	3,7948E-10	2,4176E-07	2,7579E-06	6,9679E-06	6,9679E-06
Δ pAi	0,15	3,81E-37	1,0719E-18	5,8344E-14	4,2622E-12	1,8601E-11	1,1611E-11
Δ pAi	0,2	2,96E-50	5,0895E-29	1,6881E-22	6,9321E-20	3,7441E-19	6,9321E-20
Δ pAi	0,25	4,27E-64	7,2043E-41	7,7528E-33	1,194E-29	4,3462E-29	7,6438E-31
Δ pAi	0,3	9,7E-79	3,9328E-54	6,3017E-45	1,9429E-41	1,9429E-41	6,3017E-45
Δ pAi	0,35	2,91E-94	8,8513E-69	8,7879E-59	2,3478E-55	1,8839E-56	1,1206E-62
Δ pAi	0,4	9,5E-111	7,7199E-85	1,8063E-74	1,4484E-71	1,8063E-74	7,7199E-85

# aff	150						
# non aff	850						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	2,16E-20	0,00994614	0,04896055	0,08358651	0,10417953	0,11025423
Δ pAi	0,1	2,01E-39	5,571E-07	0,00010149	0,00058665	0,00119145	0,00139743
Δ pAi	0,15	1,11E-58	2,7555E-13	8,462E-09	2,9851E-07	1,2395E-06	1,6229E-06
Δ pAi	0,2	3,27E-78	2,1683E-21	3,2211E-14	1,1049E-11	1,111E-10	1,5638E-10
Δ pAi	0,25	4,96E-98	4,4952E-31	6,5226E-21	3,1015E-17	2,5169E-16	1,1763E-15
Δ pAi	0,3	3,7E-118	3,6987E-42	8,129E-29	6,9335E-24	5,4331E-22	6,5657E-22
Δ pAi	0,35	1,4E-138	1,6797E-54	7,1058E-38	1,2938E-31	2,9415E-29	2,5869E-29
Δ pAi	0,4	2,4E-159	5,4915E-68	4,8846E-48	2,1003E-40	1,3332E-37	6,8178E-38

# aff	affected individuals
# non aff	non affected individuals
pAi non aff	allele frequency in non affected individuals
Δ pAi	% Difference in allele frequency between affected and non-affected individuals

Figure 3 (II)

09680390 - 032003

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MAR 2 0 2003
OIPE
JC194

p-VALUE DISTRIBUTION

# aff	200						
# non aff	500						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	1,06E-12	0,00789803	0,03942584	0,06867566	0,08621572	0,09083704
Δ pAi	0,1	3,45E-24	4,4217E-07	5,6883E-05	0,00031976	0,0006363	0,00070881
Δ pAi	0,15	5,9E-36	4,3025E-13	3,3635E-09	9,2134E-08	3,319E-07	3,5871E-07
Δ pAi	0,2	4,73E-48	1,5566E-20	1,0346E-14	1,7218E-12	1,1512E-11	1,0047E-11
Δ pAi	0,25	1,67E-60	3,5436E-29	2,0473E-21	2,2178E-18	1,1498E-17	1,3524E-17
Δ pAi	0,3	2,46E-73	7,2498E-39	3,0748E-29	2,0601E-25	3,4525E-24	7,4807E-25
Δ pAi	0,35	1,44E-86	1,6945E-49	3,9559E-38	1,4118E-33	2,662E-32	1,4118E-33
Δ pAi	0,4	3,2E-100	5,3051E-61	4,7325E-48	7,1282E-43	1,0691E-41	7,2652E-44

# aff	500						
# non aff	1000						
	pAi non aff	0	0,1	0,2	0,3	0,4	0,5
Δ pAi	0,05	6,48E-24	5,7827E-05	0,00172627	0,00551541	0,00882876	0,00978249
Δ pAi	0,1	6,53E-47	3,065E-14	1,0301E-09	4,3205E-08	1,8833E-07	2,2731E-07
Δ pAi	0,15	1,2E-70	2,0716E-27	3,7441E-19	4,6626E-16	6,9719E-15	6,9719E-15
Δ pAi	0,2	3,33E-95	1,1636E-43	1,6614E-31	8,5632E-27	4,1421E-25	1,9885E-25
Δ pAi	0,25	1,2E-120	1,7683E-62	1,5329E-46	3,1722E-40	8,6765E-39	3,6071E-39
Δ pAi	0,3	5,3E-147	1,526E-83	4,2697E-64	2,5968E-56	3,9328E-54	2,5968E-56
Δ pAi	0,35	2,4E-174	1,184E-106	4,5658E-84	4,7426E-75	4,2624E-73	4,0958E-77
Δ pAi	0,4	9,4E-203	1,082E-131	2,137E-106	1,8014E-96	3,3252E-95	6,725E-102

# aff	affected individuals
# non aff	non affected individuals
pAi non aff	allele frequency in non affected individuals
Δ pAi	% Difference in allele frequency between affected and non-affected individuals

Figure 3 (III)

09659289 .032003

OIPE JC134 MAR 2 0 2003 PATENT & TRADEMARK OFFICE

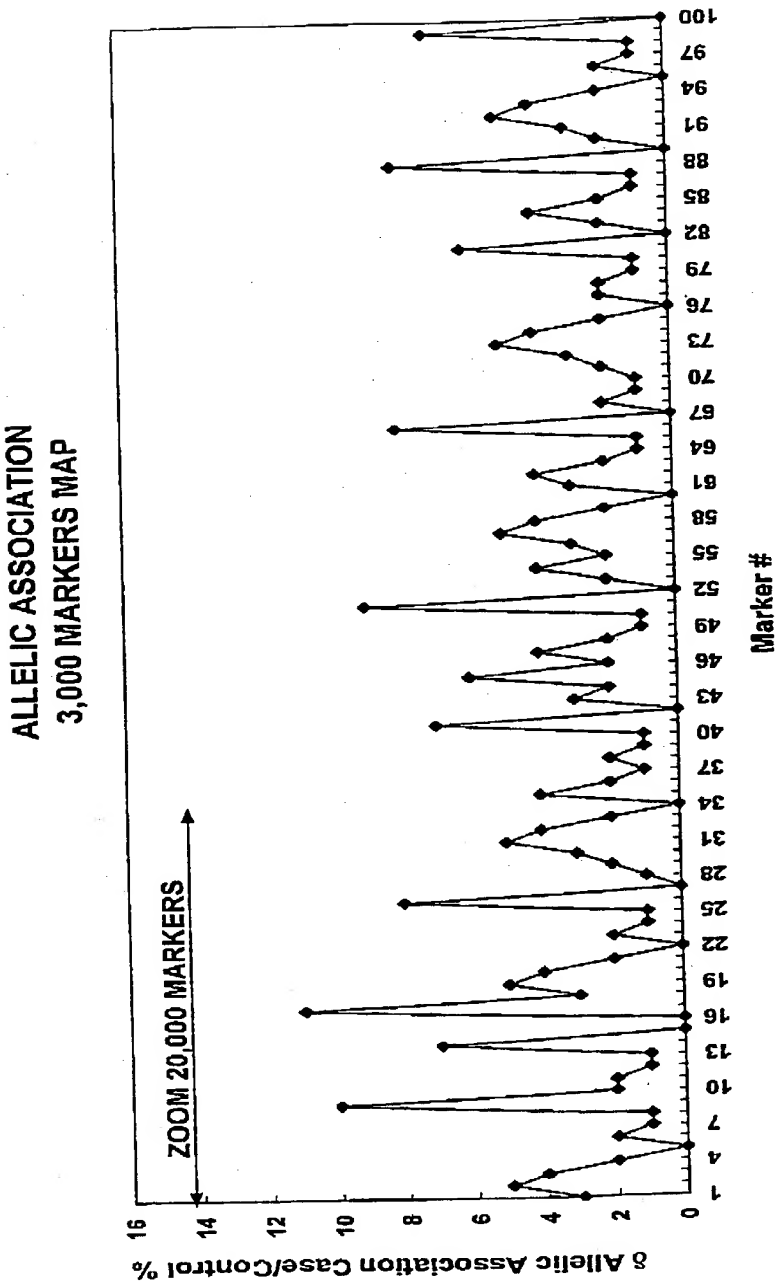

Figure 4

OIPE
JC184
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

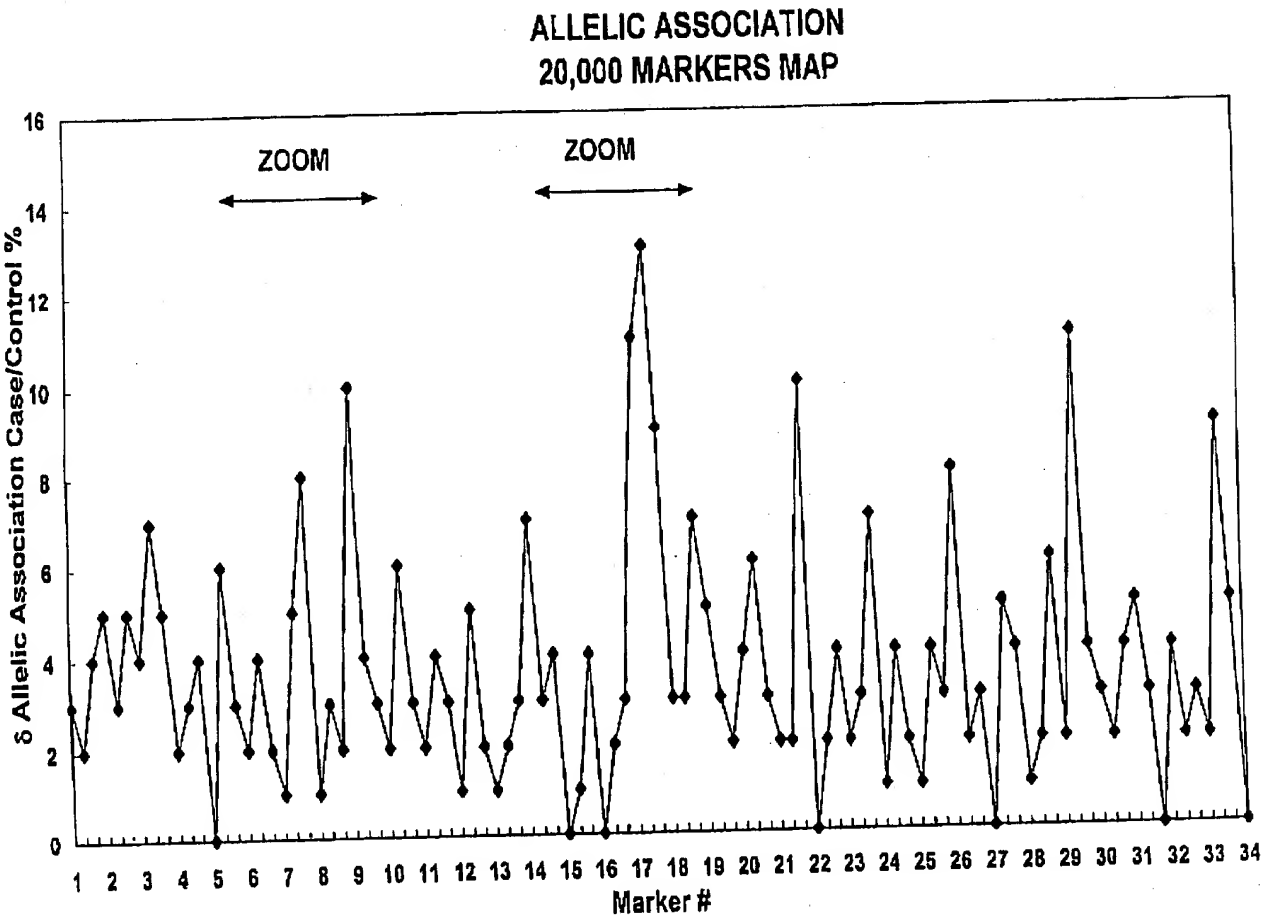

Figure 5

PATENT & TRADEMARK OFFICE
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OIPE
JC194

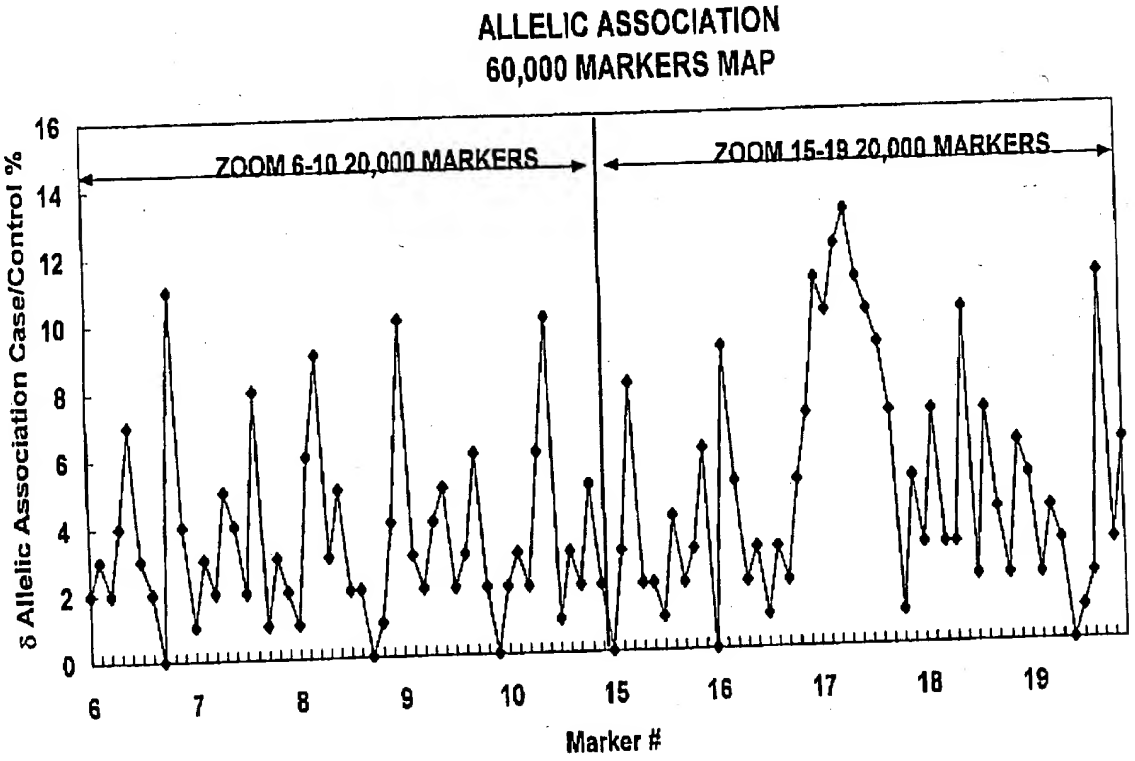

Figure 6

PATENT & TRADEMARK OFFICE MAR 2 0 2003 OIPE JC194

APO E REGION HAPLOTYPE FREQUENCY ANALYSIS

POPULATIONS	AD CASES (225)	AD CONTROLS (248)

markers	99-366	99-344	99-359	99-355	haplotype frequencies		odds-ratio	P value
p value	3,01E-01	1,11E-01	6,63E-01	1,38E-01	cases	controls		
haplotype 1	C	G			0,404	0,308	1,52	3,05E-03 ***
haplotype 2		G	A		0,203	0,165	1,29	1,24E-01 *
haplotype 3			G	G	0,375	0,306	1,36	2,83E-02 **
haplotype 4	C		A		0,264	0,209	1,36	5,95E-02 **
haplotype 5		G		A	0,115	0,071	1,70	1,64E-02 **
haplotype 6	C			A	0,15	0,129	1,19	3,59E-01 *
haplotype 7	T		G	G	0,225	0,122	2,09	4,76E-05 *****
haplotype 8	T	A	G	G	0,228	0,108	2,44	2,05E-06 ******

Figure 7

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MAR 2 0 2003
OIPE
JC134

APO E REGION HAPLOTYPE SIMULATION
POPULATION : 225 CASES vs 248 CONTROLS

	4 Markers				haplotype frequencies		odds-ratio	pvalue
	99-344/439	99-366/274	99-359/308	99-355/219	cases	controls		
Haplotype 8	A	T	G	G	0,228	0,108	2,44	2,05E-06 ******

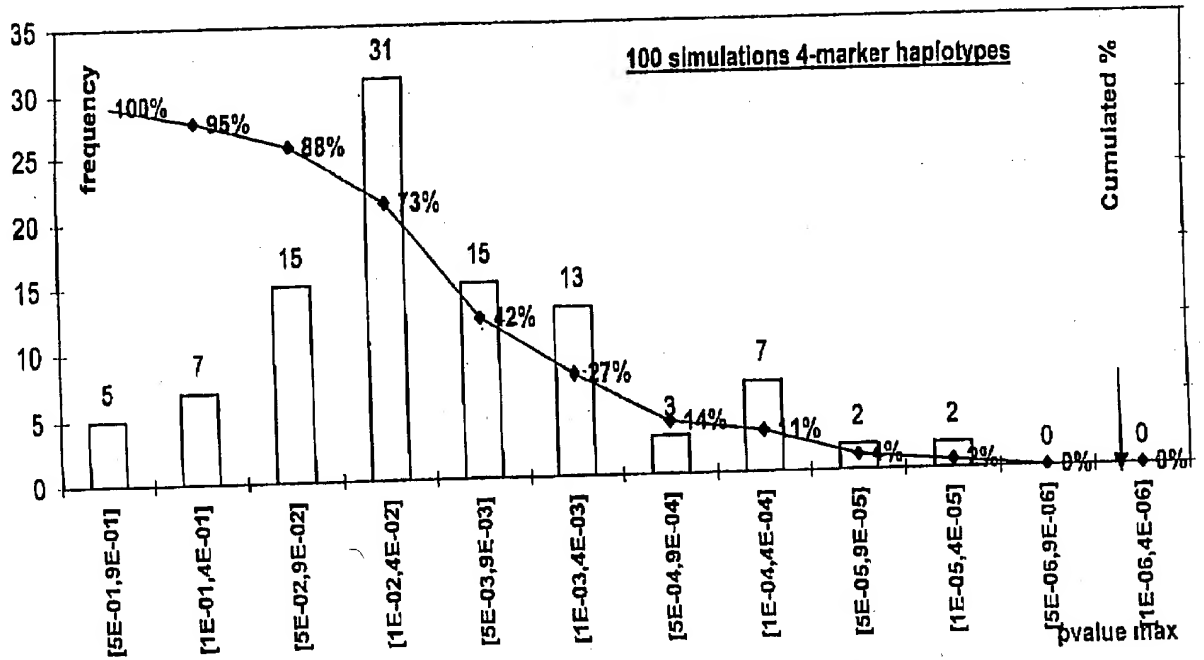

Figure 8

09855289 .032003

OIPE JC184
2 0 2003
TRADEMARK OFFICE

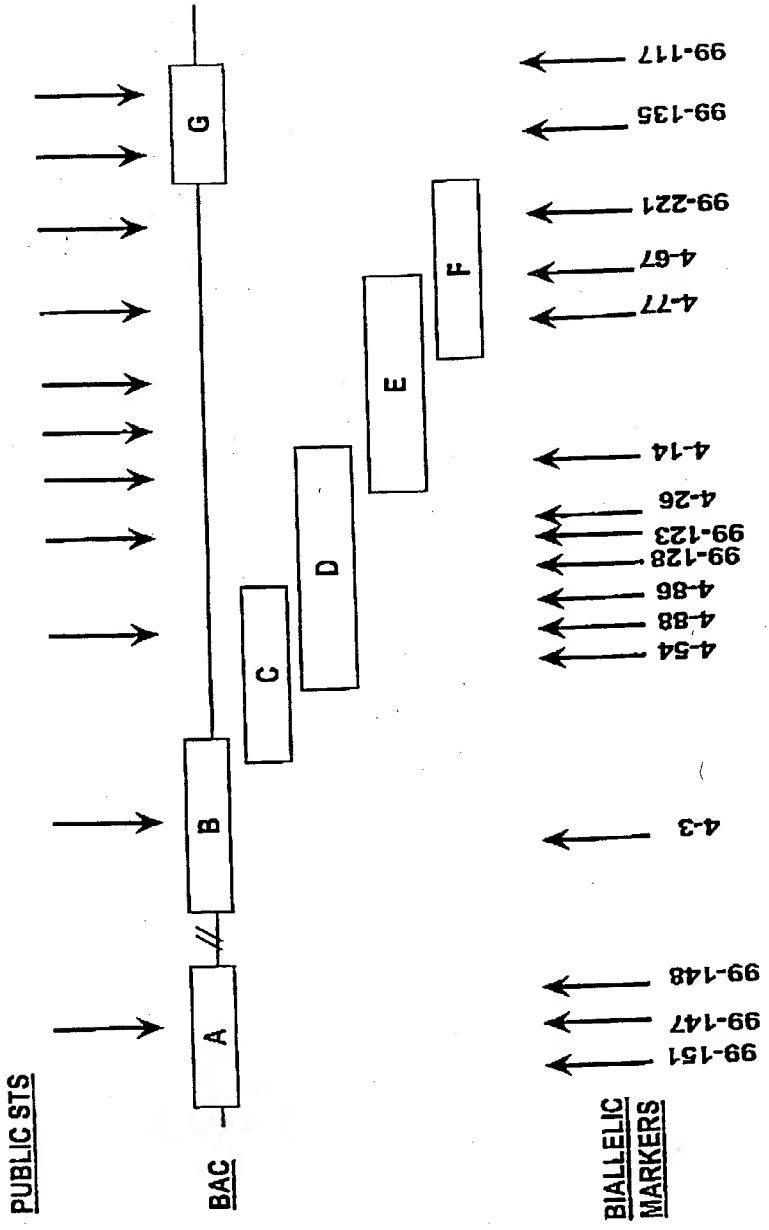

Figure 9

PATENT & TRADEMARK OFFICE
MAR 2 0 2003
OIPE
JC194

PROSTATE CANCER ASSOCIATION STUDIES (FIRST SCREENING)

Population Sample size	PROSTATE CANCER CASES = 112	NON AFFECTED CONTROLS=76
Population Characteristics	35 sporadic cases + 77 familial cases	> 65 years PSA<4

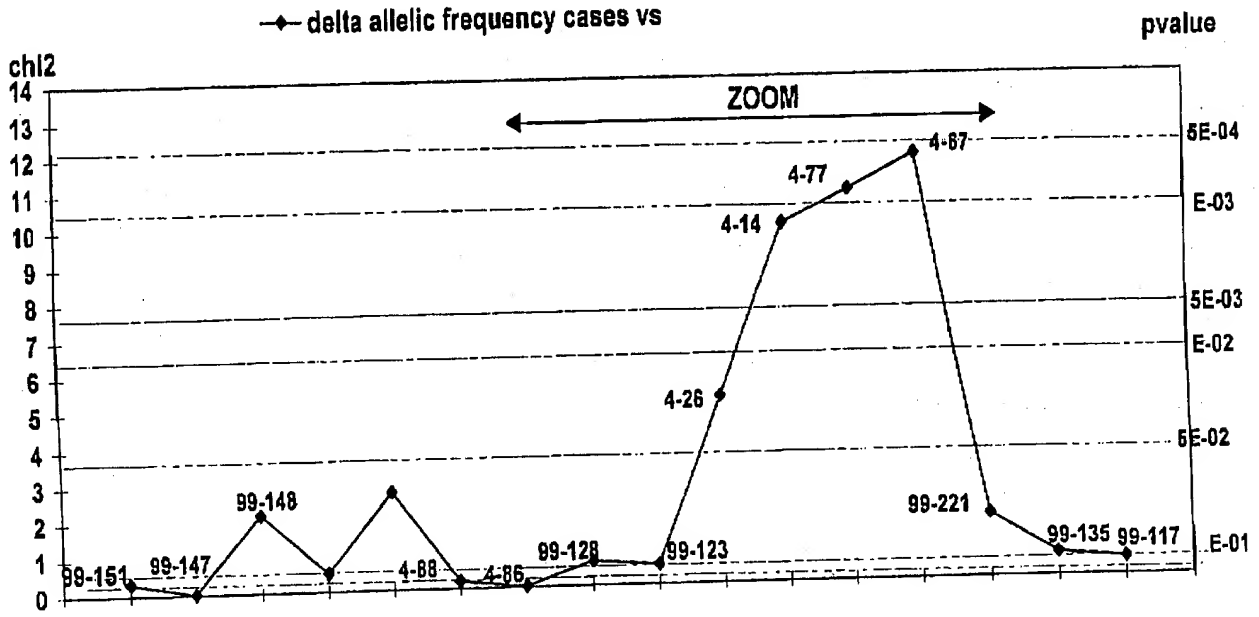

Figure 10

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JC134

PROSTATE CANCER ASSOCIATION STUDIES (ZOOM)

	PROSTATE CANCER CASES (185)	NON-AFFECTED CONTROLS (104)
characteristics of populations	47 sporadic cases + 138 familial cases	> 65 years PSA<4

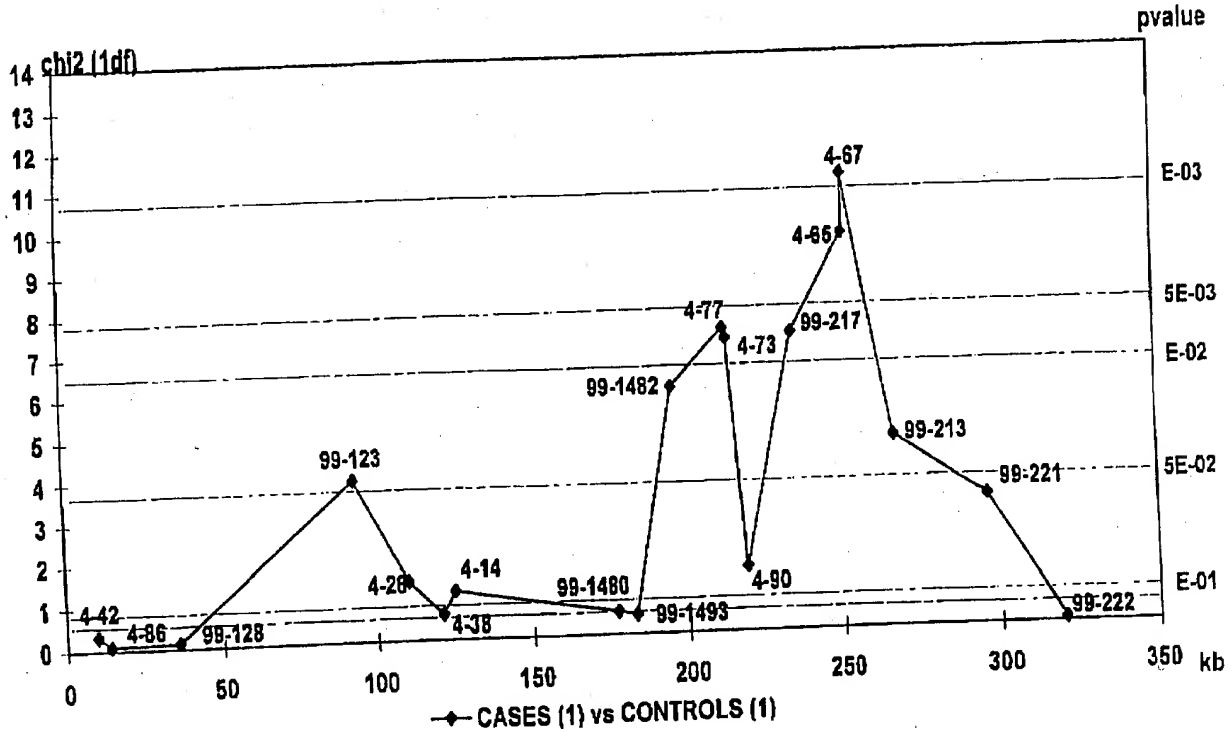

Figure 11

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OIPE
JC194

PROSTATE CANCER HAPLOTYPE FREQUENCY ANALYSIS

	PROSTATE CANCER CASES (281)	NON-AFFECTED CONTROLS (130)
characteristics of populations	143 sporadic cases + 138 familial cases	> 65 years PSA<4

markers	99-123	4-26	4-14	4-77	99-217	4-67	99-213	99-221	99-135	haplotype frequencies		relative risk	pvalue
bacs	H0287B09	B0189E08		B0463F01					B0725B12				
genes	<----PG1---->												
p value	2,00E-01	1,00E-01	1,00E-01	2,00E-02	2,00E-02	6,00E-04	9,00E-02	7,00E-01	2,00E-01	cases	controls		
haplotype 8 >304kb<	C	A	C	G	T	T	C	A	A	0,075	0,018	4,42	9,00E-04 ***
haplotype 7 >286kb<		A	C	G	T	T	C	A	A	0,095	0,016	6,46	6,00E-05 ****
haplotype 6 <186kb>		A	C	G	T	T	C	A		0,116	0,019	6,78	1,00E-05 *****
haplotype 5 <171kb>			C	G	T	T	C	A		0,117	0,013	10,06	9,00E-07 ******
haplotype 4 <83kb>				G	T	T	C	A		0,117	0,025	5,17	2,00E-05 *****
haplotype 3.1 <54kb>					T	T	C	A		0,117	0,027	4,78	2,00E-05 *****
haplotype 3.2 <54kb>				G	T	T	C			0,222	0,109	2,33	4,00E-05 *****
haplotype 2.2 <39kb>				G	T	T				0,251	0,134	2,17	2,00E-04 ****
haplotype 2 <32kb>					T	T	C			0,226	0,112	2,32	1,00E-04 ****
haplotype 1.1 <17 kb>					T	T				0,256	0,148	2,01	3,00E-04 ****
haplotype 1.2 <15 kb>						T	C			0,233	0,129	2,05	6,00E-04 ***

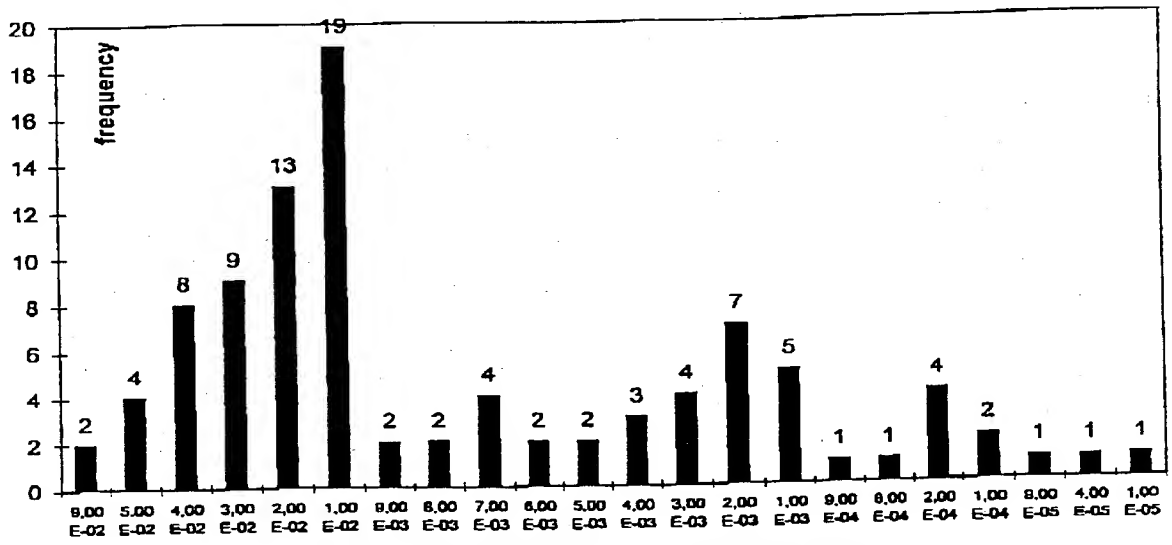
Figure 12

09855269 .032003

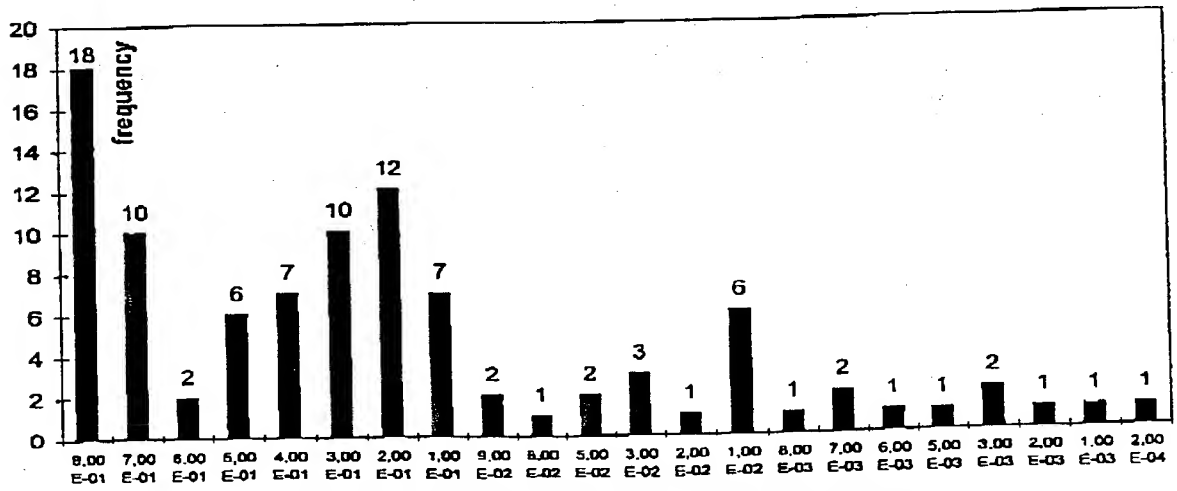
OIPE JC194
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

PROSTATE CANCER HAPLOTYPE SIMULATIONS (100 ITERATIONS)

							haplotype frequencies		relative risk	pvalue
markers	4-14	4-77	99-217	4-67	99-213	99-221	cases	controls		
haplotype	C	G	T	T	G	A	0,117	0,013	10,06	9,00E-07



pvalue max of haplotypes for 100 simulations



pvalue of haplotype CGTTGA for 100 simulations

Figure 13

OIPE JC194 MAR 2 0 2003 PATENT & TRADEMARK OFFICE

AVERAGE LD PATTERN GENOMIC HETEROGENEITY

Recombination rate	Lower A	Higher B
Nb markers	89	69
All SNP	0.61 (749)	0.42 (1190)
Rare < 0.2 Rare vs rare	0.75 (65)	0.17 (158)
Frequent > 0.2 Frequent vs frequent	0.51 (410)	0.49 (544)
Rare vs frequent	0.72 (274)	0.41 (488)

FIGURE 14

09958259.032003

OIPE JC194 MAR 2 0 2003 PATENT & TRADEMARK OFFICE

Exonic/nonexonic LD

	Nb pairs	Average intermarker distance	Average LD
Exonic SNPs	36	26 kb	0.65±0.021
Non exonic SNPs	60	36 kb	0.48±0.018
Exonic/Non exonic	96	32 kb	**0.60±0.015**

FIGURE 15

09858259 .032003

OIPE JC154
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

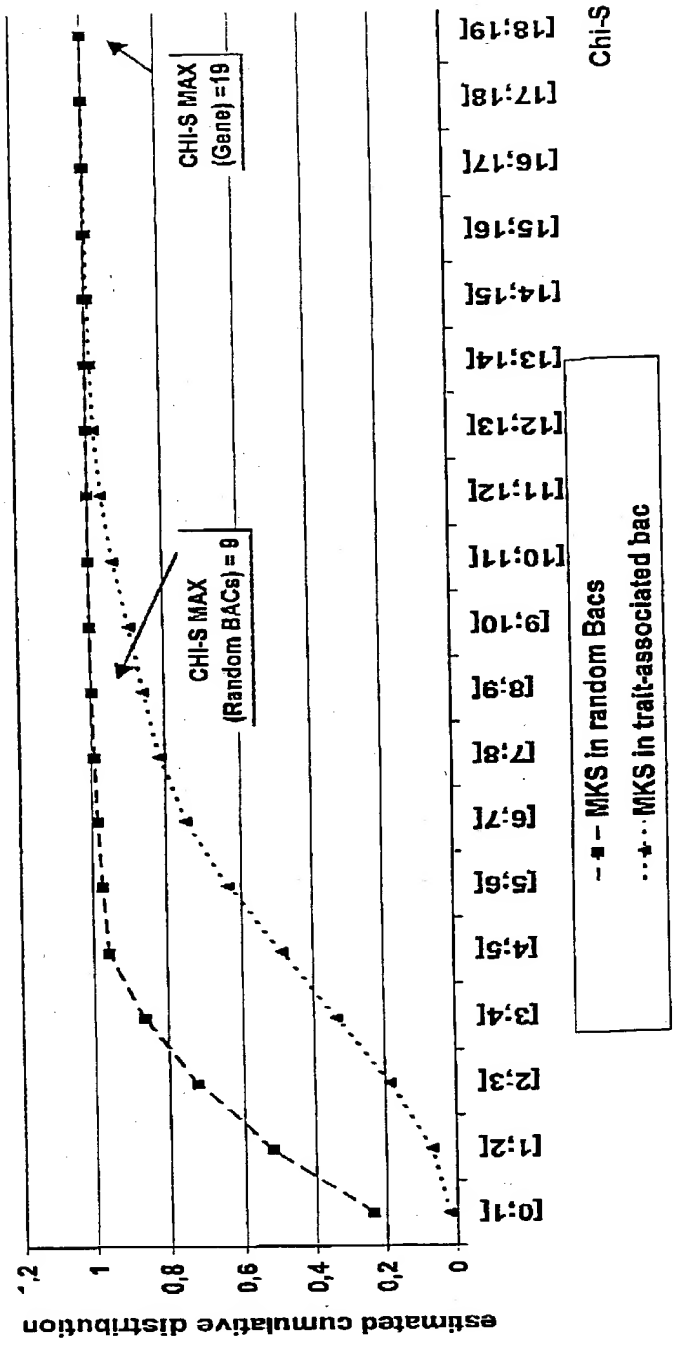


FIGURE 16 A

09850289 . 032003

OIPE JC194
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

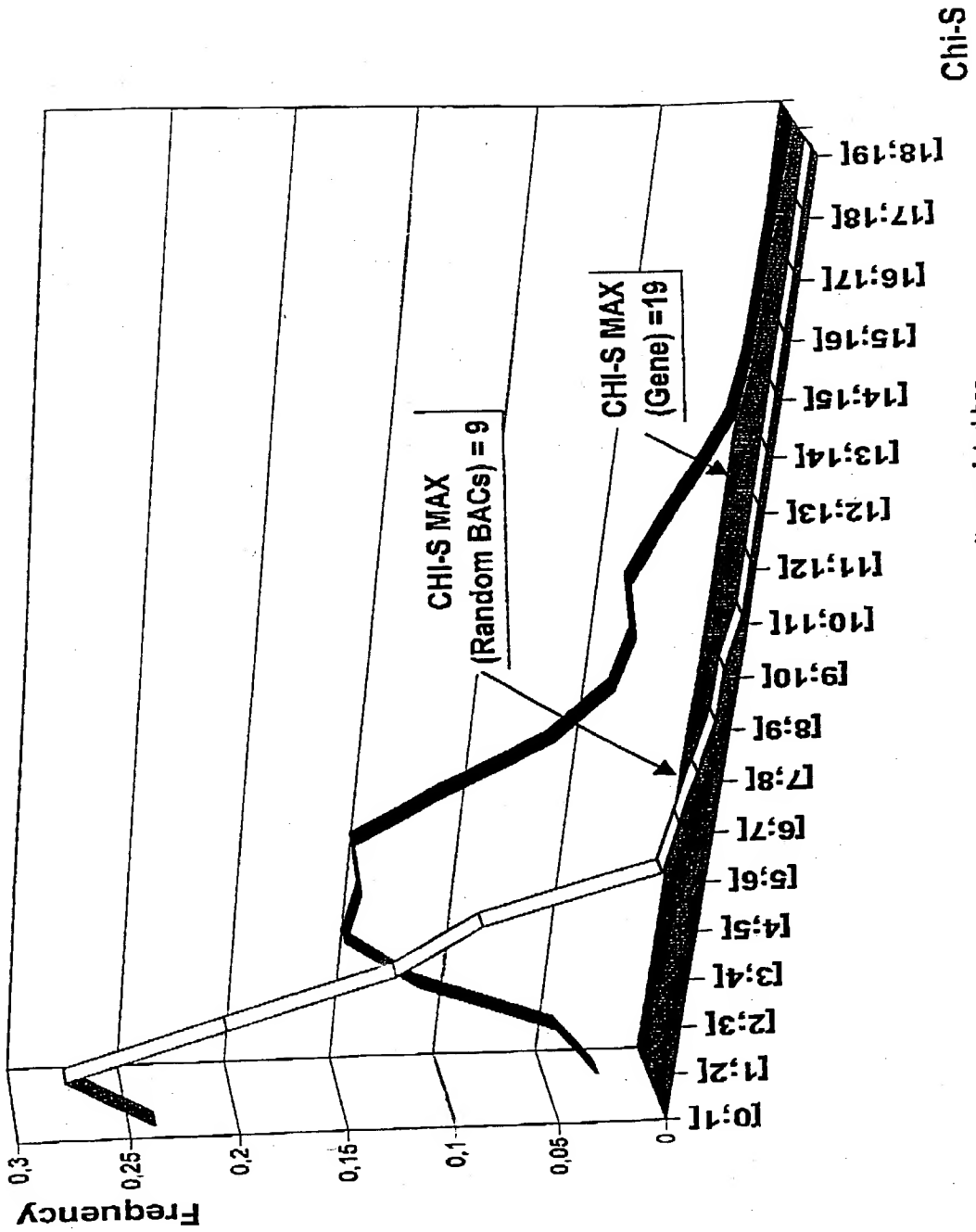


FIGURE 16B

OIPE JC194
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

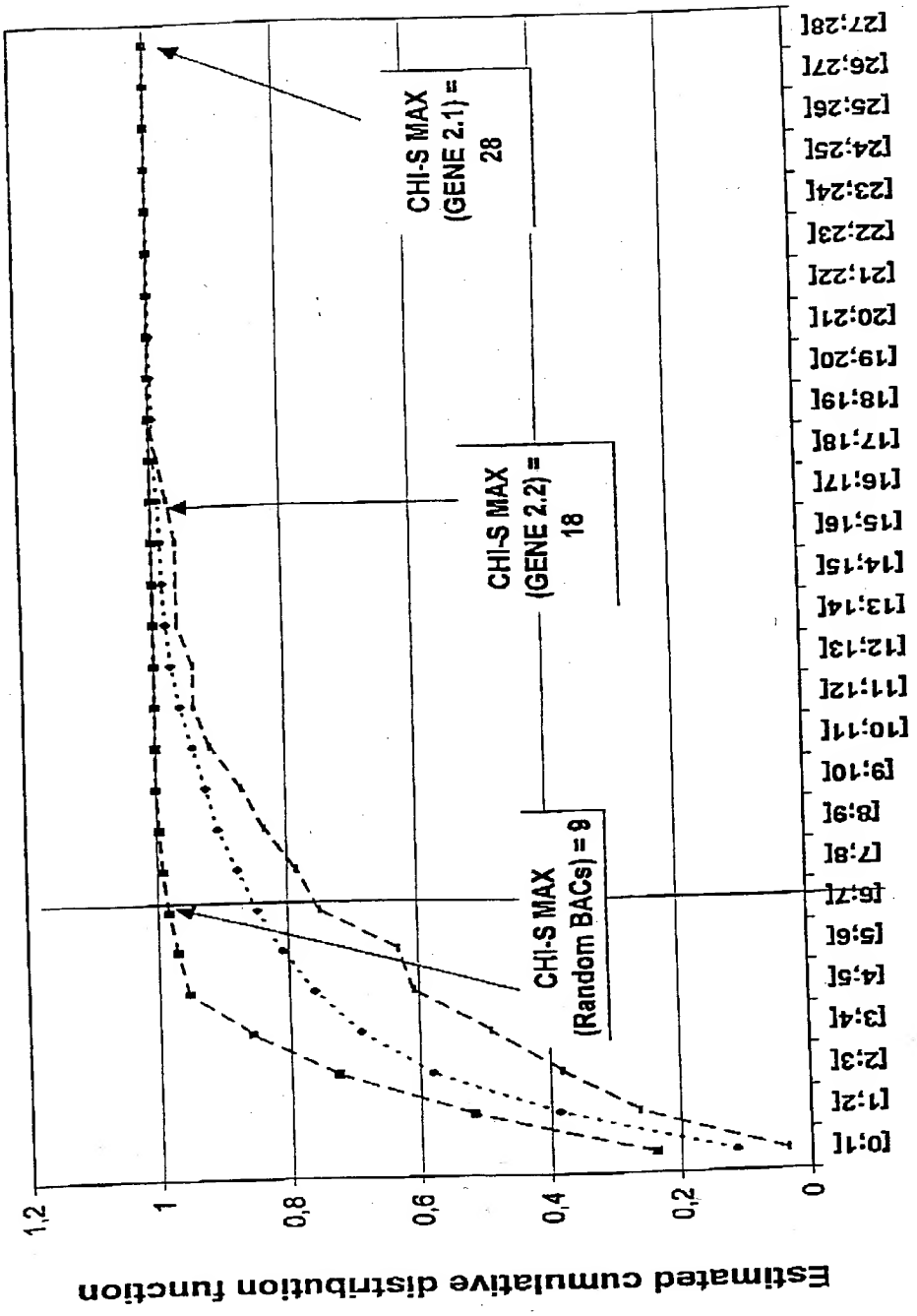


FIGURE 17A

09858289 .032003

OIPE JC164
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

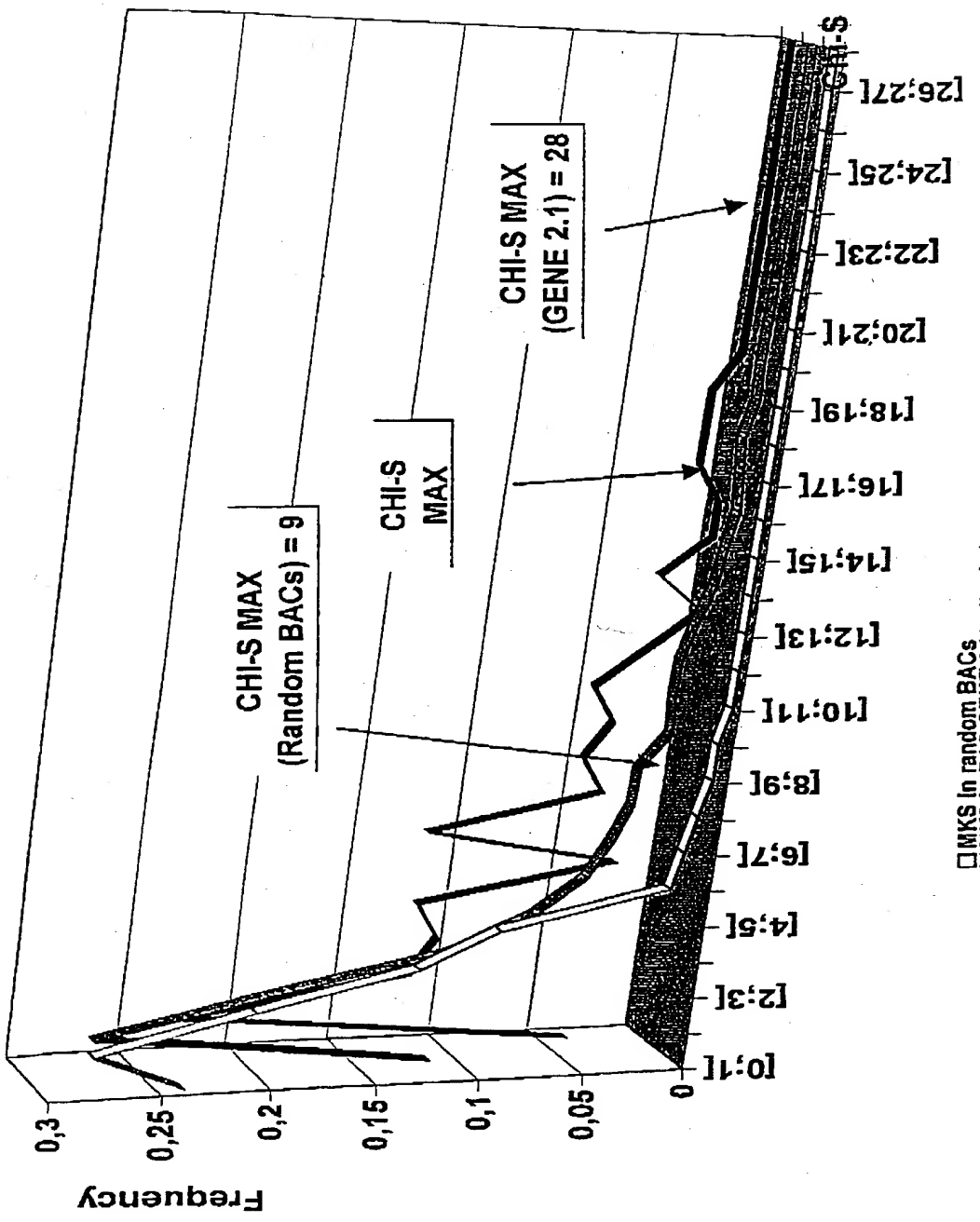


FIGURE 17 B

09859289 .032003

OIPE JC194 MAR 2 0 2003 PATENT & TRADEMARK OFFICE

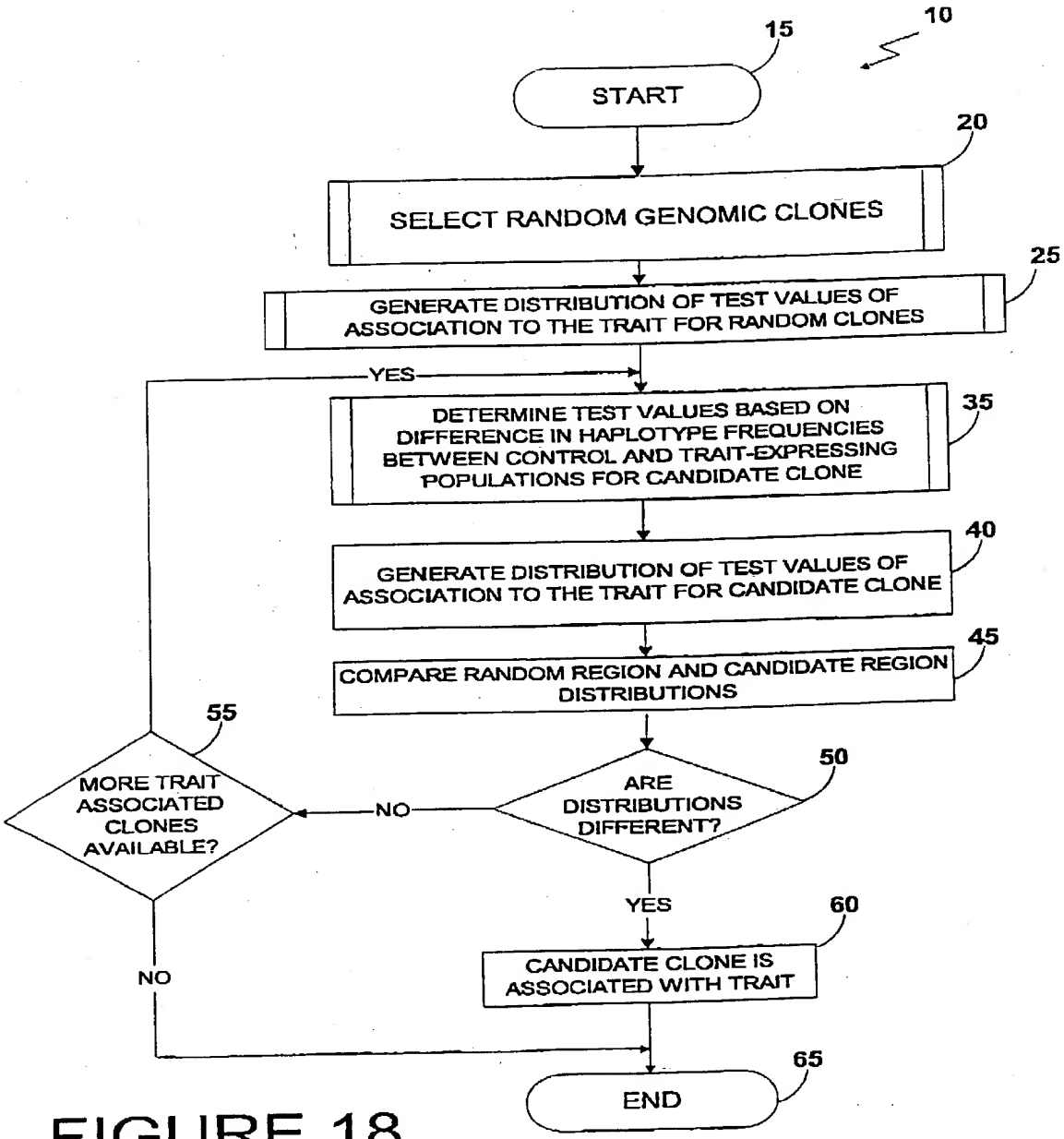


FIGURE 18

09853289.032003

OIPE JC194
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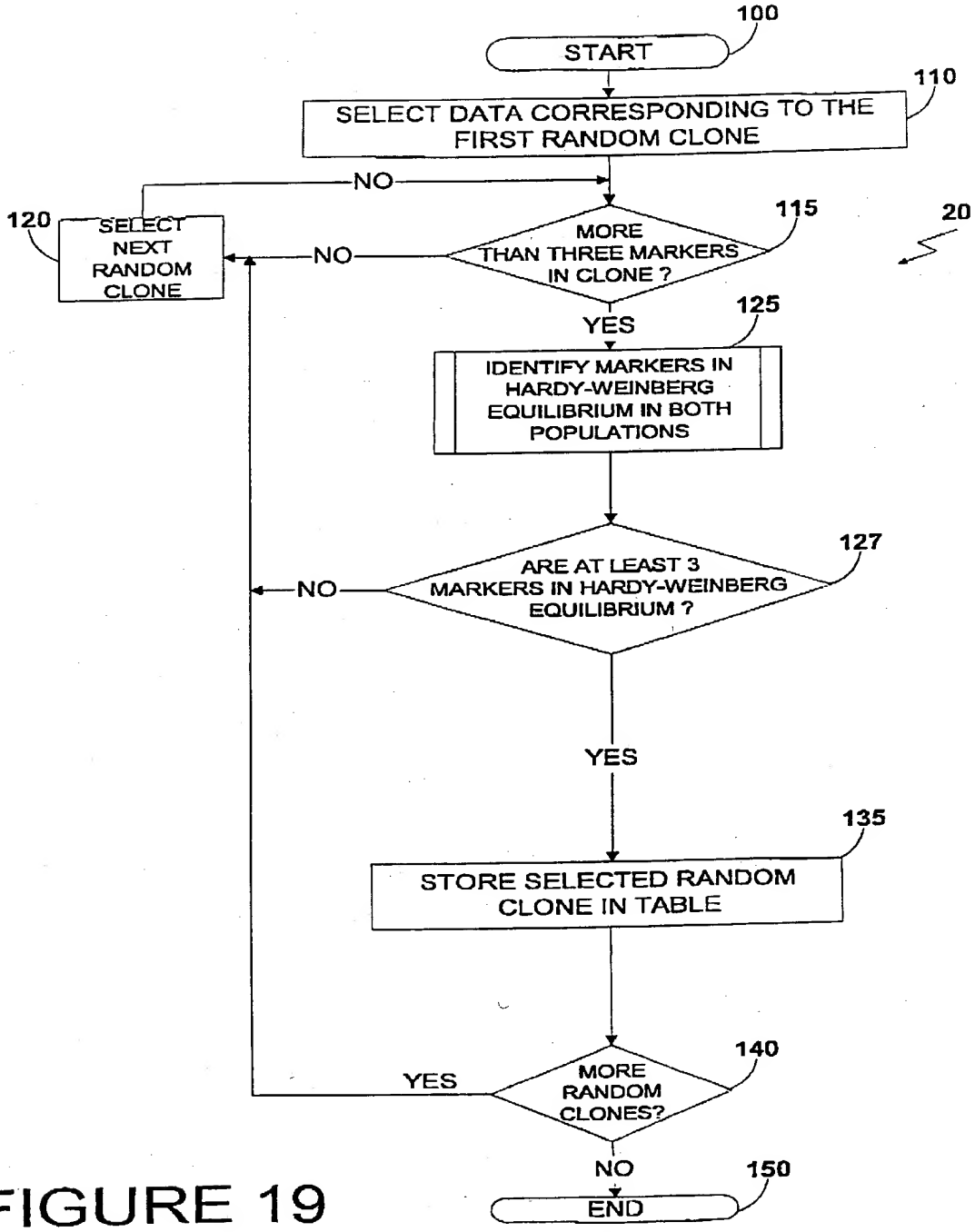

FIGURE 19

09/658289 .032003

OIPE #4
MAR 2 0 2003
PATENT & TRADEMARK OFFICE
JC134

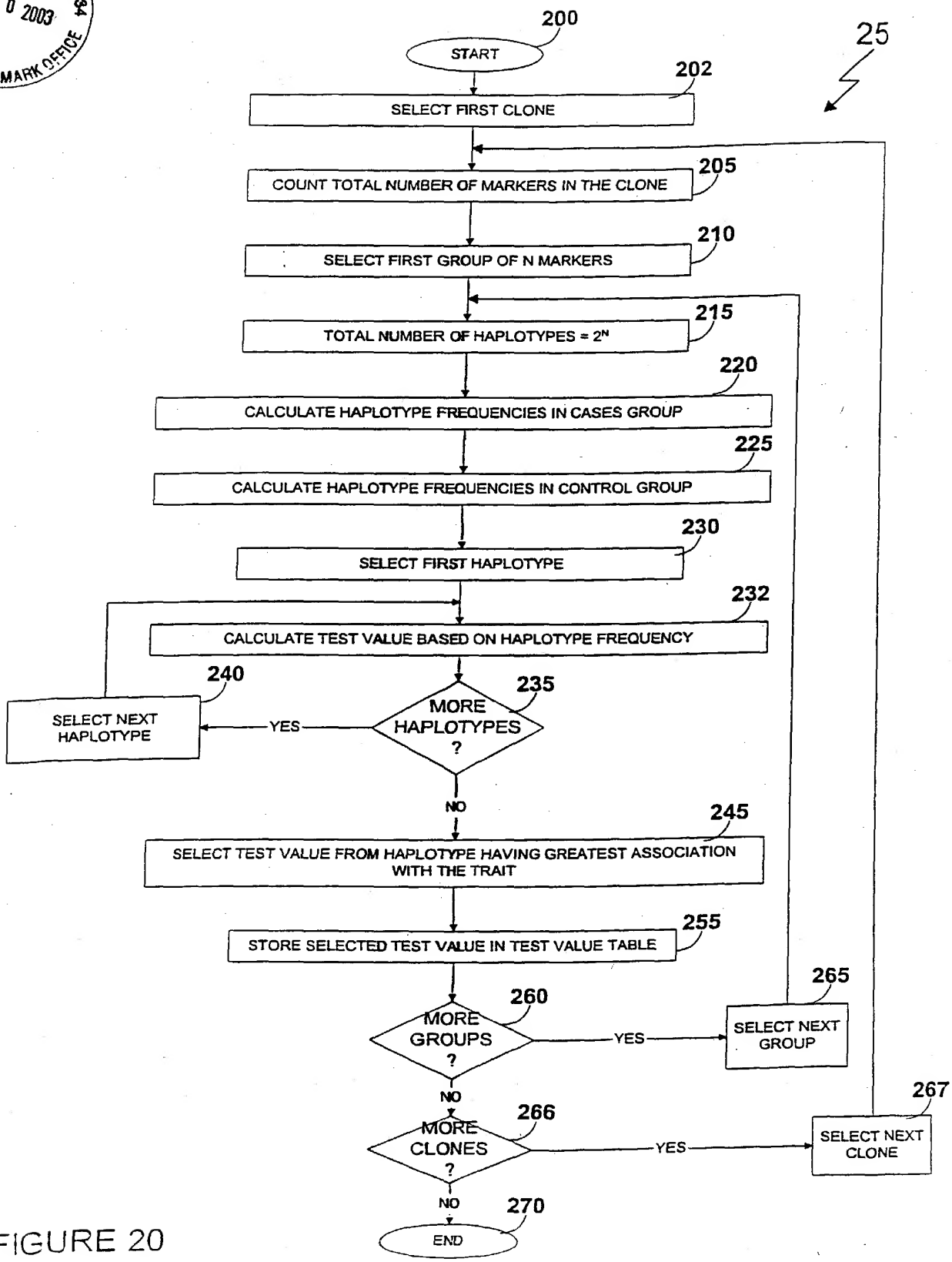

FIGURE 20

09658239.032003

OIPE JC194
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

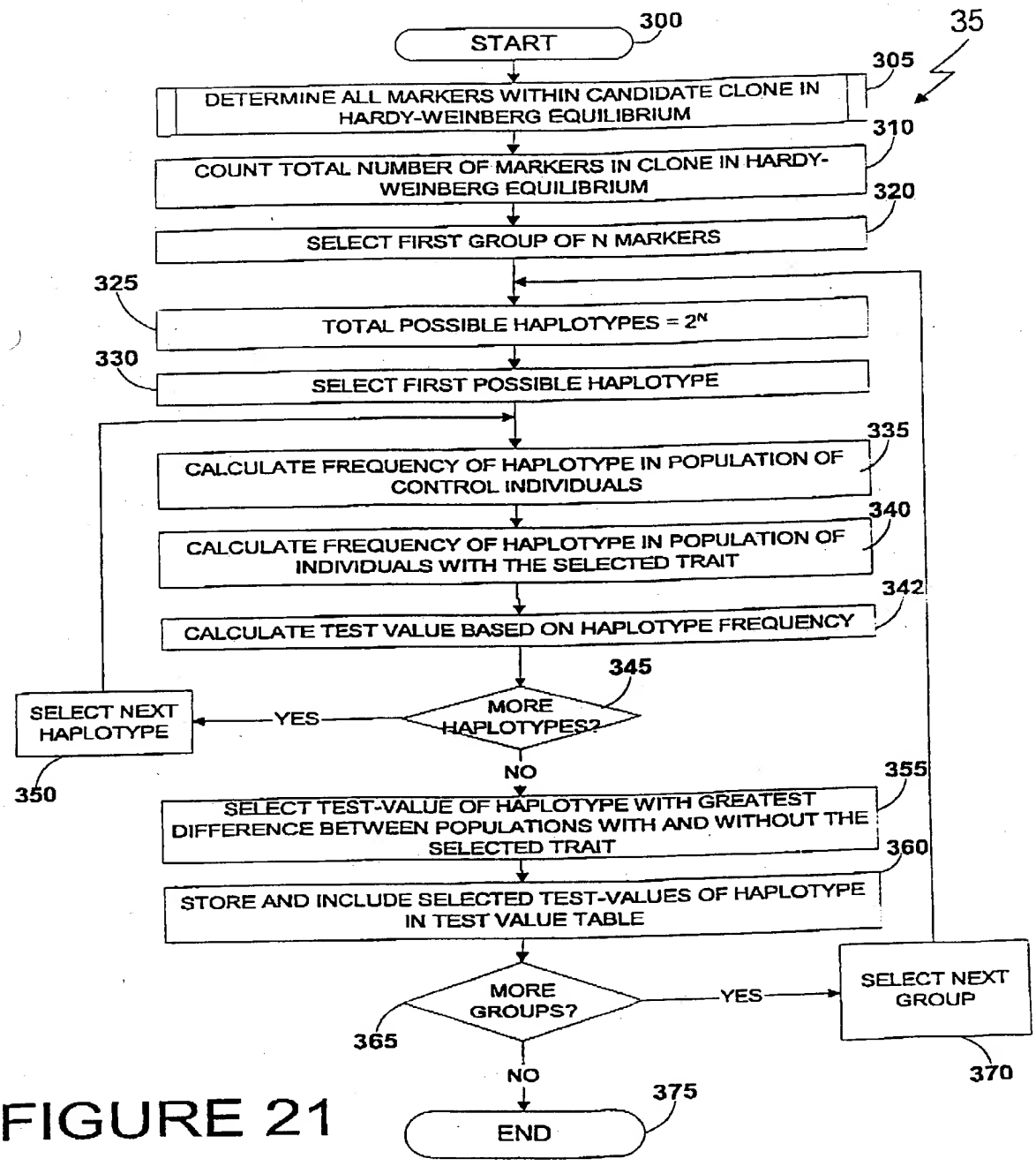

FIGURE 21

09553289.032003

OIPE JC184 MAR 20 2003 PATENT & TRADEMARK OFFICE

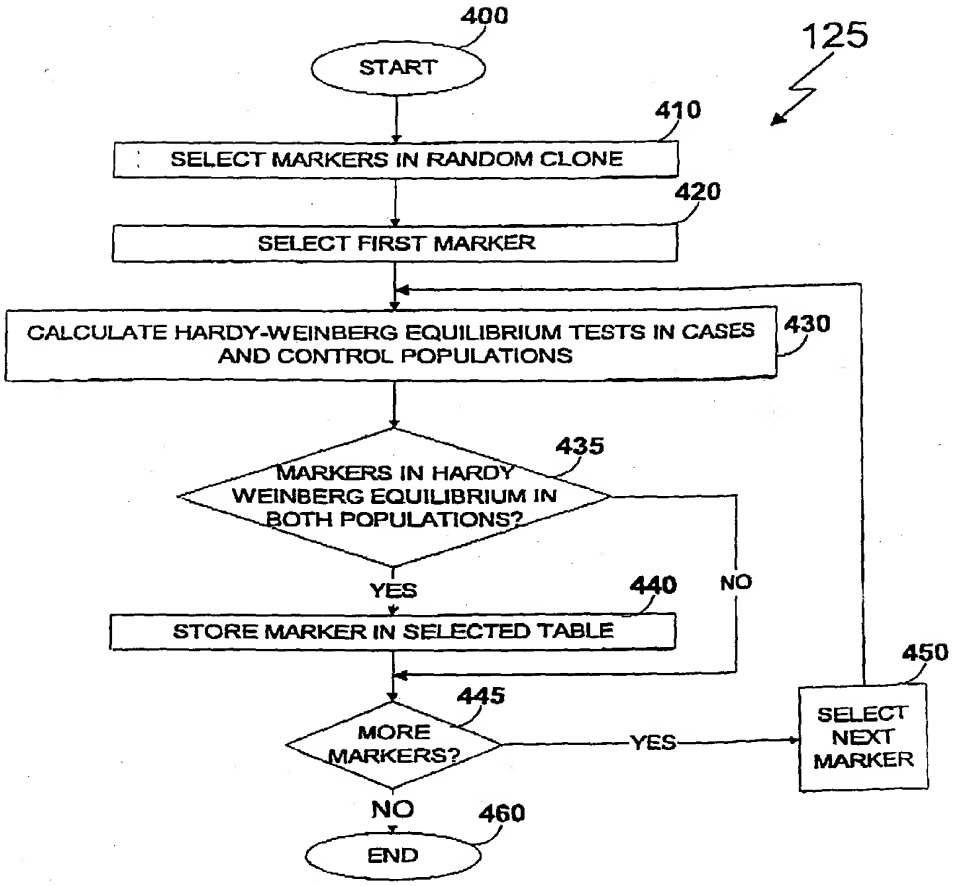

FIGURE 22

OIPE JC134 MAR 2 0 2003 PATENT & TRADEMARK OFFICE

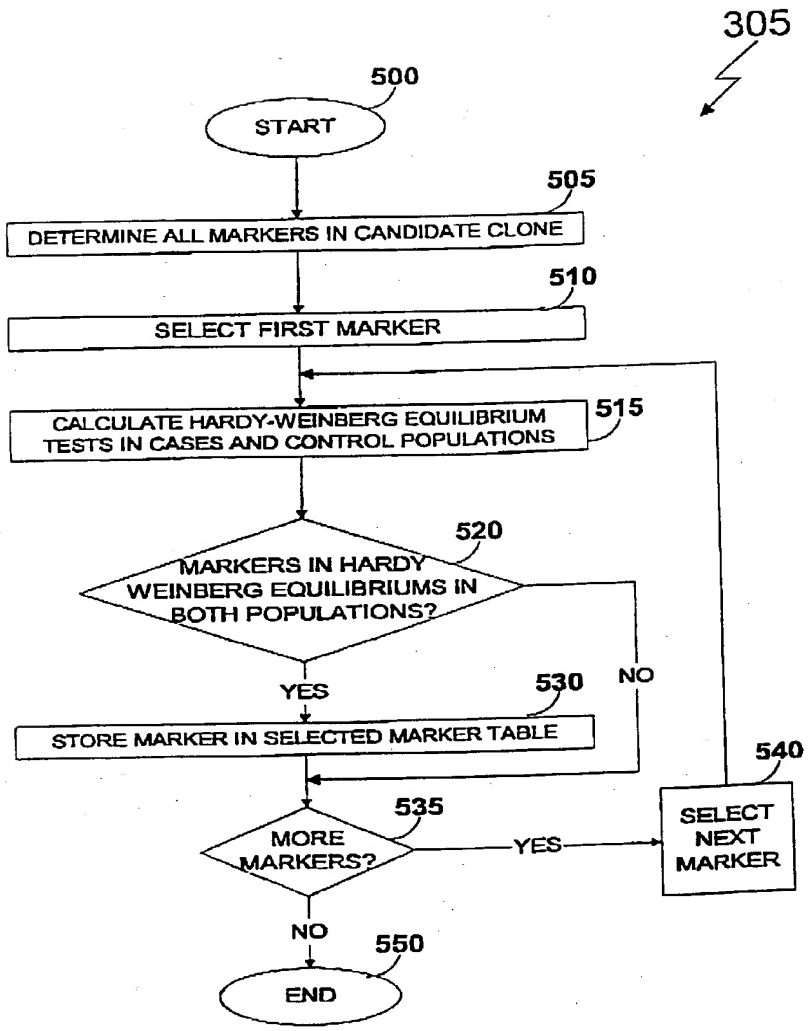

FIGURE 23

09958290.032003

OIPE JC194
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

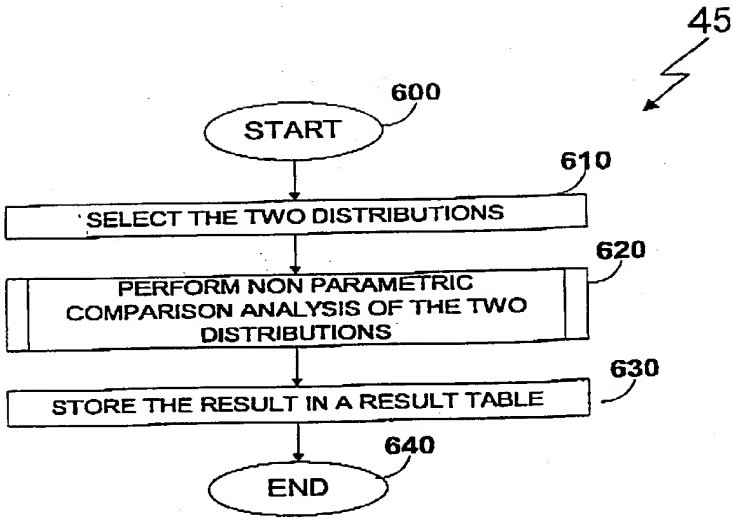

FIGURE 24

OIPE JC194
MAR 2 0 2003
PATENT & TRADEMARK OFFICE

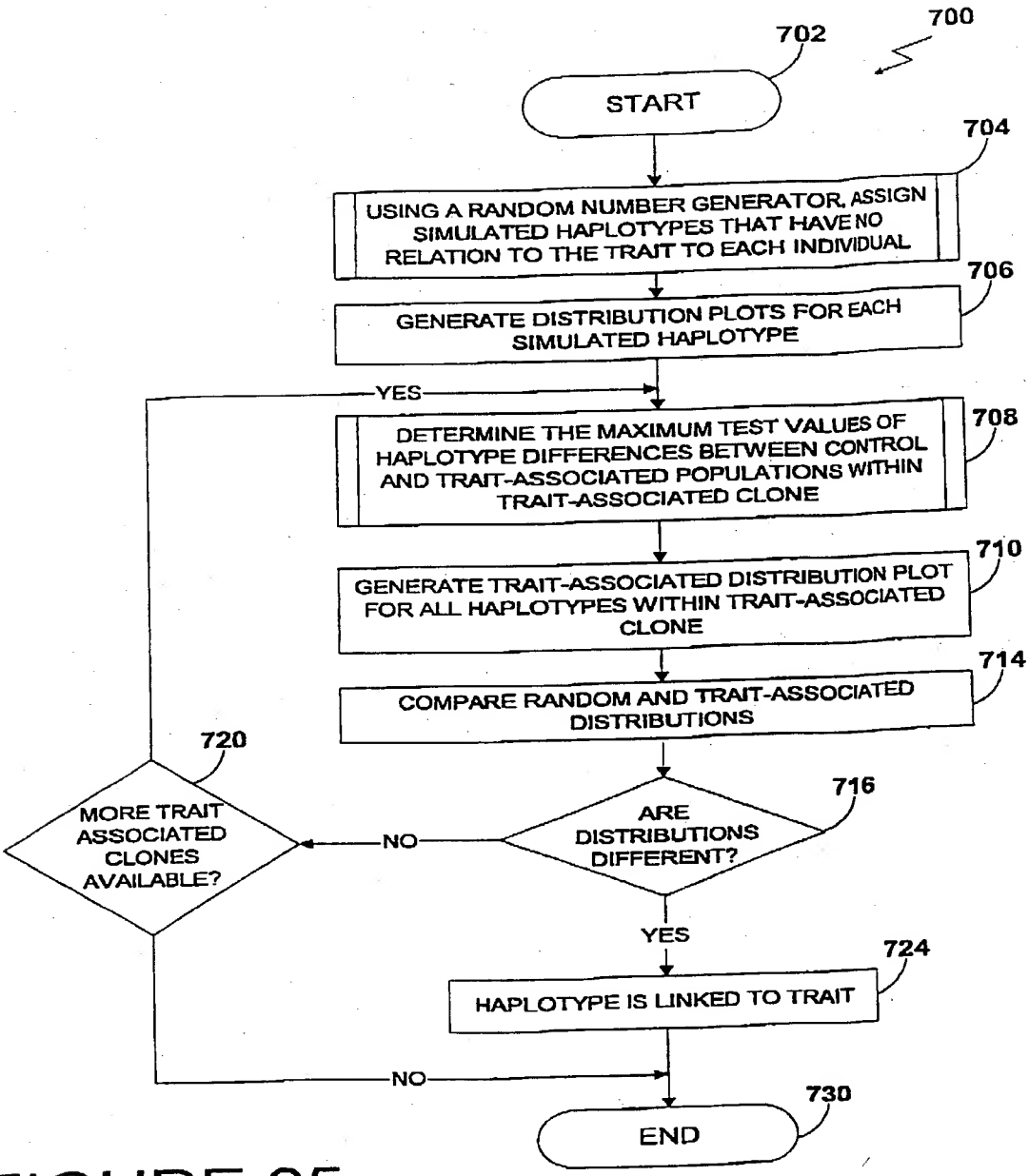

FIGURE 25